REMARKS

This submission is in response to the Official Action dated January 3, 2002. Claim 1 has been canceled, without prejudice or disclaimer. Claims 2 and 4 have been amended. The Examiner has withdrawn claims 6-13 have been from further consideration under 37 C.F.R. 1.142(b). Thus, claims 2-5 are pending and at issue. No new matter has been added by this amendment. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Claim 2 has been amended to independent form, and to recite that the hNPRAP polypeptide comprises a C-terminal armadillo-like repeat and can be a full-length hNPRAP or a biologically active hNPRAP analogue. This amendment is fully supported by the specification as filed, *e.g.*, by the description of hNPRAP and its analogues on page 4, lines 7-10, and page 5, lines 16-27.

Claim 4 has been amended to change its dependency from canceled claim 1 to claim 2.

Each of the Examiner's objections and rejections are addressed below.

Sequence Requirements

The Examiner contends that the specification does not describe and reference SEQ ID NOS: 1 and 2.

Applicants respectfully direct the Examiner's attention to page 7, lines 7

and 8, where SEQ ID NOS: 1 and 2 are described and referred to. This objection should therefore be withdrawn.

Written Description

The Examiner has rejected claims 1-2 and 4-5 as allegedly not complying with the written description requirement. Specifically, the Examiner contends that the specification does not adequately describe sequences from other species, mutated sequences, allelic variants, splice variants, and homologous sequences that are encompassed within the claims.

Contrary to the Examiner's contentions, however, the specification provides both the nucleotide and amino acid sequences of an hNPRAP homologue, namely the murine hNPRAP homologue (SEQ ID NOS: 5 and 6, respectively).

In addition, as amended, the claims recite that the hNPRAP polypeptide comprises a C-terminal armadillo-like repeat and is a full-length hNPRAP or a biologically active hNPRAP analogue. The specification amply describes the features of such hNPRAP polypeptides (page 4, lines 7-10 and page 5, lines 17-24):

> The human Neural Plakophilin Related Armadillo Protein ("hNPRAP") (also described as GT24) consensus cDNA (SEQ ID NO:3) encodes a protein (SEQ ID NO:4) of 1084 amino acid residues with a unique N-terminus, but with homology to proteins with armadillo (arm) repeat motifs at its C-terminus.
>
> An "hNPRAP" is defined herein as a biologically active polypeptide that contains a sequence of hNPRAP that mediate its nerve cell growth stimulating activity, *e.g.*, the armadillo repeats. Thus, hNPRAP includes full-length (naturally occurring) hNPRAP, as well as biologically active

analogues thereof. By "analogues" it is meant modifications such as point mutations, amino acid substitutions, additions or deletions, or other mammalian homologues, such as mouse (SEQ ID NO:5 and SEQ ID NO:6), which have similar activity to hNPRAP, the identification and selection of which are well-known to those skilled in the art.

Thus, one of ordinary skill in the art, provided with the hNPRAP nucleotide and amino acid sequences of SEQ ID NOS: 3 and 4 and the murine homologues of SEQ ID NOS; 5 and 6, respectively, could easily envision the hNPRAP polypeptides used in the method of the invention. The method of the invention employs full-length hNPRAP and hNPRAP analogues that are defined both by structural features such as sequence homology or identity to SEQ ID NOS: 4 and/or 6 and the presence of armadillo-like repeats, and by functional features such as nerve-growth stimulating activity.

Accordingly, the amended claims comply with the written description requirement, and reconsideration and withdrawal of this rejection is respectfully requested.

Enablement

Claims 1-5 have been rejected as allegedly not enabled by the specification. Specifically, the Examiner contends that the specification does not disclose cell types that exhibit a response to hNPRAP, show evidence of neuronal regeneration, or disclose activities for the divergent molecules encompassed by the claims.

Applicants respectfully disagrees. The specification discloses methods for stimulating nerve cell growth, neuronal regeneration, and synapse formation using hNPRAP polypeptides (see specification, *e.g.*, at page 3, lines 6-15; page 4, lines 11-16; page 5, lines 16-24; page 6, lines 1-8; and page 7, line 24to page 8, line 2). Moreover, the nucleotide and amino acid sequences of both human hNPRAP and an murine hNPRAP homologue are provided. A person of skill in the art, armed with these sequences, could easily search for and identify hNPRAP proteins and polypeptides useful in the method of the invention. For example, any protein sequence containing armadillo-like repeats could be compared to SEQ ID NO:4 to assess whether the protein sequence is an hNPRAP mutant or other analogue. Such evaluations are well-known and frequently practiced in the art, using freeware or commercially available software. If the protein is found to be a mutant or other analogue of SEQ ID NOS:4 and/or 6, it could then be tested for hNPRAP nerve-growth stimulating activity using, *e.g.*, the experimental procedures described on page 7, line 24, to page 8, line 2. While such experimental procedures might be laborious, they do not constitute undue experimentation. As described in the MPEP, section 2164.01, "[t]he fact that experimentation may be complex does no necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F/2d at 737, 8 USPQ2d at 1404.

Further, the Examiner appears to believe that the specification states that the neuronal regeneration and axon-sprouting activity of hNPRAP is solely due to the armadillo-like repeat (Office Action, page 6, 1st full paragraph), referring to page 5, lines 16-28 of the specification. The Examiner then notes that the literature discloses armadillo proteins but fail to recognize neuronal growth as a function of such proteins (Paffenholz et al.).

However, firstly, the lack of disclosure in the Paffenholz et al. reference merely emphasizes the surprising nature of the method of the invention; that hNPRAP polypeptides, of which one feature is a C-terminal armadillo-like repeat, are capable of stimulating nerve-cell growth. Secondly, the invention is by no means bound to the armadillo-like repeats being solely responsible for the nerve-growth stimulating capability of hNPRAP polypeptides. As set forth in the specification in the section referenced by the Examiner, a "hNPRAP" is a "biologically active polypeptide that contains **a** sequence that mediate[s] its nerve cell growth stimulating activity, ***e.g.***, the *armadillo* repeats" (emphasis added). The method defined by the pending claims employs full-length hNPRAP or hNPRAP analogues that comprises a C-terminal armadillo-like repeat. Accordingly, the armadillo-like repeat is only one of the structural features that defines the polypeptides used in the method of the invention.

The Examiner also cites a reference by Skolnick et al., which teaches that

even a single amino acid substitution may lead to functional changes in biological activity (Skolnick et al.), using this citation as support for the allegation that the specification "fails to teach the purported activities for the divergent molecules as encompassed by the claims." Applicant assumes that the "purported activities" referred to by the Examiner is stimulation of nerve cell growth.

The Skolnick et al. reference relates to proteins in general, not to cell growth-stimulatory proteins, thus being of limited applicability to the field of the invention. However, even if applied to the correct field, Applicants fail to see how Skolnick's teachings impact the enablement of the invention. The claimed method is a method using a hNPRAP polypeptide having nerve growth stimulating activity. Since this is a functional feature of the hNPRAP polypeptides used, and since the invention is, in fact, a method for stimulating nerve cell growth, hNPRAP polypeptides not possessing this activity are not of interest.

Accordingly, Applicants submit that the invention as set forth by the pending claims is enabled, and respectfully requests reconsideration and withdrawal of this rejection.

Indefiniteness

The Examiner has rejected claims 1-2 and 4-5 for alleged indefiniteness, contending that the specification fails to teach the structural meets and bounds of the generic recitation of hNPRAP.

The term "hNPRAP" is defined in the specification at page 5, lines 17-24, cited above. As amended, the claims call for hNPRAP polypeptides having nerve growth stimulating activity and comprising a C-terminal armadillo-like repeat, which hNPRAP polypeptides is selected from full-length hNPRAP and hNPRAP analogues. The structural meets and bounds of hNPRAP polypeptides used in the claimed method thus include (1) an armadillo-like repeat, (2) nerve growth stimulating activity, as well as either (3a) full-length hNPRAP, exemplified by SEQ ID NOS: 4 and 6; or (3b) an biologically hNPRAP analogue which has similar activity to hNPRAP and is an hNPRAP modified by point mutation; amino acid substitution, addition, or deletion; or is a homologue. All of these modifications are well-known in the art. Therefore, Applicants respectfully submit that the skilled artisan can readily discern the scope of the hNPRAP polypeptides employed in the present invention, and that this rejection should be withdrawn.

Novelty

The Examiner has rejected claims 1-2 and 4-5 as being anticipated by U.S. Patent 5,475,088 to Perez-Polo et al. ("Perez-Polo").

Perez-Polo relates to neurotrophic peptides, defined by certain amino acid sequences. However, Perez-Polo does not teach or suggest that his peptides are hNPRAP polypeptides, or that they comprise a C-terminal *armadillo*-like repeat. In fact, Perez-Polo fails to mention anything about *armadillo* repeats.

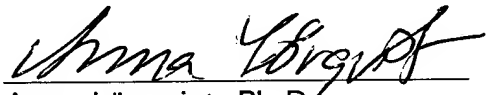
If a reference is indeed anticipatory, it must teach each and every aspect of the claimed invention either explicitly or impliedly (MPEP 706. 02). Since the hNPRAP polypeptides used in the method of the invention all comprise a C-terminal armadillo-like repeat, Perez-Polo does not anticipate the claimed invention. Accordingly, in view of the above arguments and amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

* * *

Therefore, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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Limited Recognition Under 37 C.F.R. §10.9(b) (see attached)
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PATENT TRADEMARK OFFICE

Docket No: 1034/1F811US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Peter H. ST. GEORGE-HYSLOP; Paul E. FRASER

Serial No.: 09/501,171 Art Unit: 1647

Filed: February 9, 2000 Examiner: S. TURNER

For: PROTEIN RELATED TO NEURONAL REGENERATION AND USES THEREOF

MARK-UP FOR RESPONSE TO OFFICIAL ACTION

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

March 12, 2002

Sir:

IN THE CLAIMS:

Please amend the claims pursuant to 37 C.F.R. 1.121 as follows:

2. (Amended) A method of stimulating growth of nerve cells, which method comprises contacting nerve cells with a human Neural Plakophilin Related *Armadillo*

Protein (hNPRAP) polypeptide having nerve growth stimulating activity in an amount effective to cause nerve cell growth [The method according to claim 1], wherein the hNPRAP polypeptide comprises a C-terminal armadillo-like repeat and is selected from a full length hNPRAP and a biologically active hNPRAP analogue.

4. (Amended) The method according to claim [1] 2, wherein the growth of nerve cells results in neuronal regeneration.